

JUN 9 1999

K983842

**ATTACHMENT I**  
**REVISED 510(k) SUMMARY**

## 510(k) Summary of Information Respecting Safety and Effectiveness

### A. Name and Address of Submitter

Company Name and Address: Biotest Diagnostics Corporation  
66 Ford Road, Suite 131  
Denville, NJ 07834

Telephone: (609) 397-8511

FAX: (609) 397-8224

Contact Person: Patricia E. Bonness, Official Correspondent

Date 510(k) Summary was Prepared: October 26, 1998

### B. Device Names

Proprietary Name: Biotest Anti-EBV Recombinant  
EA IgM

Common Name: EBV EA IgM

Classification Name: Epstein-Barr virus serological reagents

### C. Legally Marketed Device

Biotest Diagnostics claims substantial equivalence to the EBV IgM Test (K822734) currently in commercial distribution by Gull Laboratories, Inc., Salt Lake City, UT.

### D. Device Description

Using recombinant DNA technology, Biotest has developed three highly purified EBV antigens for use in their ELISA test system.

- EBNA-1 p72: Major antigen of the EBNA complex. The recombinant protein does not contain the glycine-alanine copolymer, a structural feature of EBNA-1, which shows cross-reactivities with certain autoantibodies and CMV (IgM response).
- EA-D p64: Early antigen. Dominant immunogen of the EA-D complex.
- EA p138: Early antigen and major DNA binding protein. This highly reactive antigen is not detectable in EA immunofluorescence assays based on chemically induced Raji cells (deletion within the Raji genome).

### Biotest Anti-EBV ELISA TESTS

Biotest Anti-EBV recombinant	recombinant antigens			monoclonal secondary antibody (HRP-conjugated)	
	p72	p54	p134	anti-human IgG	anti-human IgM
EA IgM		X	X		X
EA IgG		X	X	X	
EBNA IgG	X			X	

The EBV immune status will be determined by the detection of specific antibodies directed against EBV proteins according to the principle of the indirect ELISA. The antigens are purified to apparent homogeneity and immobilized on the solid phase (microtest plate, 96 wells). If the patient's serum contains specific antibodies they will bind during the first incubation. Non-specific antibodies are removed by washing steps. During a second incubation the captured IgM antibodies are labeled. This is performed by addition of murine monoclonal anti-human IgM antibody-enzyme-conjugates. The final reaction converts a colorless substrate to a colored product. The concentration of color after a definite time is related to the concentration of antibody in the serum sample.

#### E. Intended Use

The Biotest EA IgM ELISA is an enzyme immunoassay using recombinant antigens for the qualitative detection of IgM antibodies to the Epstein-Barr Virus early antigens (EA) p54 and p138 in human serum or plasma. Results obtained with this test, in conjunction with other clinical and patient data obtained in assays for other Epstein-Barr virus-specific antibodies such as anti-Early Antigen IgG and anti-EBNA-1 IgG, assist in serological diagnosis of EBV infection in pediatric and adult populations.

F. Comparison with Predicate Device

A summary comparison of the features of the Biotest EA IgM and the Gull VCA IGM test kits is provided in Table 1 below:

**Table 1**  
Feature Comparison of Biotest and Gull EBV IgM Test Kits

	<u>Biotest</u>	<u>Gull</u>
Intended Use	Detection of IgM antibodies to EBV EA Qualitative only	Detection of IgM antibodies to EBV VCA Qualitative only
Assay Method	ELISA	Indirect fluorescent antibody (IFA)
Reactive Ingredients	Recombinant EBV (EA p54/p138) Peroxidase-conjugated monoclonal anti-human IgM (mouse)	HR <sub>1</sub> Burkitt's lymphocytic cells Fluorescein-labeled anti-human IgM
Specimen: Type	Serum or plasma	Serum
Min. Volume	25 µl	15 µl of 1:10 and 1:40 dilutions
Storage	2 - 8°C or -20°C	2 - 8°C/7days or -20°C
Controls	Negative Positive	Negative Positive
Chromogen	TMB	Fluorescein
Results:		
Evaluation	spectrophotometer @ 450 nm	Fluorescence microscope
Kit Size	96 tests	50 or 100 tests

## G. Performance Data

### Sensitivity/Specificity

The performance of the Biotest EA IgM ELISA was evaluated in a clinical study of 408 patient samples conducted at two geographically distinct locations. Samples were obtained from both pediatric and adult patients (ages 1 to 74) representing acute (139), late acute (34), recent past (12), past (120), reactivation (22), past/probable reactivation (11), and negative (70) disease stages of EBV infection.

Two methods were used to evaluate the performance of the Biotest EA IgM ELISA: direct comparison with commercially available or published EA IgM IFA tests, and comparison with clinical interpretation (stage of infection based on antibody patterns and clinical diagnosis at the time the specimen was drawn).

Results of the direct comparison with VCA IgM/IgG IFA for both sites combined demonstrated a relative sensitivity of 84.1% and a relative specificity of 89.4%.

**Table 1**

**Clinical Site 1  
Direct Comparison to VCA IgM/IgG IFA**

VCA IgM/IgG IFA			
	+	-	Total
Biotest +	73	13	86
Biotest -	14	108	122
Total	87	121	208

Relative Sensitivity = 83.9% (C.I. = 74.5 to 90.9%)  
Relative Specificity = 89.3% (C.I. = 83.7 to 94.8%)  
Relative Agreement = 87.0%

**Table 2**

**Clinical Site 2  
Direct Comparison to VCA IgM/IgG IFA**

VCA IgM/IgG IFA			
	+	-	Total
Biotest +	80	11	91
Biotest -	15	94	109
Total	95	105	200

Relative Sensitivity = 84.2% (C.I. = 75.3 to 90.0%)

Relative Specificity = 89.5% (C.I. = 83.7 to 95.4%)

Relative Agreement = 87.0%

**Table 3**

**Combined Site Results  
Direct Comparison to VCA IgM/IgG**

VCA IgM/IgG			
	+	-	Total
Biotest +	153	24	177
Biotest -	29	202	231
Total	182	226	408

Relative Sensitivity = 84.1% (C.I. = 78.7 to 89.4%)

Relative Specificity = 89.4% (C.I. = 85.4 to 93.4%)

Relative Agreement = 87.0%

Results based on Clinical Interpretation of all patient samples where Biotest ELISA EA IgM antibody responses matched expected serological pattern analysis for each state of infection, including - Acute, Convalescent (Late Acute or Recent Past), Past, Reactivation and Probable Reactivation/past, and Negative.

Clinical Interpretation					
	Acute	Convalescent	Past	Reactivation	Negative
Result matches Biotest	138	45	117	32	2
Result does not match Biotest	1	1	3	1	68
Sensitivity	99.2%	97.8%	97.5%	96.9%	N/A
Specificity	N/A	N/A	N/A	N/A	97.1%
95% to C.I.%	96.1 - 100	88.5 - 99.9	92.9 - 99.5	84.2 - 99.9	90.1 - 99.7

Total Clinical Sensitivity = 98.2% (C.I. = 96.2 to 99.3%)

Total Clinical Specificity = 97.1% (C.I. = 90.1 to 99.7%)

Total Clinical Agreement = 98.0%

Note: C.I. = 95% confidence intervals calculated by the exact method.

### Cross Reactivity

No cross reactivity was observed when the Biotest EA IgM ELISA was used to test samples from patients acutely infected with:

Herpes Simplex Virus I/II	4 of 5	samples found non-reactive
Varicella Zoster Virus	5 of 11	samples found non-reactive
Cytomegalovirus	3 of 9	samples found non-reactive
Toxoplasma	4 of 5	samples found non-reactive

Further, no cross reactivity was observed in tests of rheumatoid factor positive (n = 10), antinuclear antibody positive (n = 5) and ASL positive (n = 15) samples.

## Reproducibility

To evaluate the reproducibility of the Biotest EA IgM ELISA, a panel of 10 patient serum specimens (low to high positive) was tested at the clinical sites. The mean, standard deviation (S.D.) and coefficient of variation (C.V.) for inter-run, intra-run and inter-lab reproducibility are presented below.

### **Site #1**

Panel #	Inter-Run (n = 11)			Intra-Run (n = 8)		
	Mean	S.D.	% C.V.	Mean	S.D.	% C.V.
1	1.799	0.175	9.7	1.801	0.065	3.6
2	1.013	0.171	16.9	1.140	0.032	2.8
3	1.280	0.183	14.3	1.286	0.070	5.5
4	0.294	0.033	11.2	0.287	0.018	6.3
5	1.065	0.119	11.2	1.189	0.059	5.0
6	0.651	0.088	13.5	0.680	0.034	5.1
7	1.231	0.152	12.3	1.325	0.060	4.5
8	0.959	0.130	13.5	0.946	0.060	6.3
9	0.798	0.100	12.5	0.811	0.037	4.6
10	0.664	0.067	10.0	0.711	0.020	2.9

### **Site #2**

Panel #	Inter-Run (n = 5)			Intra-Run (n = 24)		
	Mean	S.D.	% C.V.	Mean	S.D.	% C.V.
1	1.641	0.127	7.7	1.829	0.268	14.7
2	1.165	0.036	3.1	1.257	0.164	13.1
3	1.415	0.043	3.1	1.471	0.124	8.4
4	0.335	0.020	6.0	0.362	0.052	14.4
5	1.271	0.063	5.0	1.372	0.127	9.3
6	0.664	0.032	4.8	0.773	0.076	9.9
7	1.360	0.083	6.1	1.522	0.104	6.8
8	1.009	0.075	7.4	1.111	0.099	8.9
9	0.932	0.037	3.9	0.997	0.070	7.0
10	0.705	0.019	2.7	0.783	0.048	6.2



**Inter-Lab (n = 14)**

Panel #	Mean	S.D.	% C.V.
1	1.75	0.172	9.8
2	1.061	0.167	15.7
3	1.322	0.173	13.1
4	0.307	0.037	11.9
5	1.129	0.140	12.4
6	0.655	0.077	11.8
7	1.271	0.153	12.0
8	0.974	0.117	12.1
9	0.840	0.110	13.1
10	0.677	0.053	7.9



JUN 9 1999

Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850

Ms. Patricia E. Bonness  
Official Correspondent  
Biotest Diagnostics Corporation  
66 Ford Road  
Suite 131  
Denville, New Jersey 07834

Re: K983842  
Trade Name: Biotest Anti-EBV Recombinant EA IgM  
Regulatory Class: I  
Product Code: LSE  
Dated: March 15, 1999  
Received: March 31, 1999

Dear Ms. Bonness:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

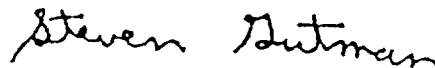
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Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770)488-7655.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or at (301) 443-6597 or at its internet address "<http://www.fda.gov/cdrh/dsmamain.html>"

Sincerely yours,

A handwritten signature in black ink that reads "Steven Gutman". The signature is written in a cursive, flowing style.

Steven I. Gutman, M.D., M.B.A.  
Director  
Division of Clinical Laboratory Devices  
Office of Device Evaluation  
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known): K983842Device Name: Biotest Anti-EBV Recombinant EA IgM

## Indications For Use:

The Biotest EA IgM is an enzyme immunoassay for the detection of IgM antibodies to the Epstein-Barr Virus (EBV-EA (Early Antigens) p54/p138) in human serum or plasma.

It is indicated for use, in conjunction with other clinical and patient data obtained in assays for other Epstein-Barr antigens such as EBNA IgG and Early Antigen IgG, in the serological diagnosis of EBV infection.

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Woody Decker  
(Division Sign Off)  
Division of Clinical Laboratory Devices  
510(k) Number K983842

Prescription Use X  
(Per 21 CFR 801.109)

OR

Over-The-Counter Use \_\_\_\_\_

(Optional Format 1-2-96)